Journal of Psychiatric Research 43 (2009) 1219–1223

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Increase in thalamic binding of [^{11}C]PE2I in patients with schizophrenia: A positron emission tomography study of dopamine transporter

Ryosuke Arakawa [a,b], Tetsuya Ichimiya [a,b], Hiroshi Ito [a], Akihiro Takano [a], Masaki Okumura [a,b], Hidehiko Takahashi [a], Harumasa Takano [a], Fumihiko Yasuno [a], Motoichiro Kato [c], Yoshiro Okubo [b], Tetsuya Suhara [a,*]

[a] Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263-8555, Japan
[b] Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan
[c] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 15 January 2009
Received in revised form 5 March 2009
Accepted 21 April 2009

Keywords:
Dopamine transporter
Schizophrenia
Thalamus
Positron emission tomography
[^{11}C]PE2I
PANSS

ABSTRACT

Previous *in vivo* imaging studies reported no difference in dopamine transporter (DAT) bindings in the striatum between control subjects and patients with schizophrenia. However, as the signals of radioligands with moderate affinity were insufficient for allowing the evaluation of small amounts of DAT, DAT binding in extrastriatal regions has not been determined. Positron emission tomography scanning using [^{11}C]PE2I was performed on eight patients with schizophrenia and twelve normal control subjects. Binding potential (BP_{ND}) for DAT in the caudate, putamen, thalamus and substantia nigra was calculated, using the cerebellum as reference region. In patients with schizophrenia, clinical symptoms were evaluated by Positive and Negative Syndrome Scale (PANSS). BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than in control subjects ($P = 0.044$). In patients with schizophrenia, there were significantly positive correlations between BP_{ND} in the thalamus and total ($r = 0.75$), positive ($r = 0.78$) and negative PANSS scores ($r = 0.82$). Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

1. Introduction

One of the most accepted hypotheses concerning the pathophysiology of schizophrenia are the hyperactivity of dopaminergic neurotransmission. This 'dopamine hypothesis' is supported by the facts that antipsychotic effects are mainly related to dopamine D_2 receptor antagonism and that dopamine stimulating agents can cause psychotic symptoms such as hallucination or delusion. Dopamine transporter (DAT) plays a role in the reuptake of dopamine into pre-synaptic nerves and regulates dopaminergic transmission in the synaptic cleft. DAT inhibitors such as cocaine increase dopamine concentration in the synaptic cleft (Schlaepfer et al., 1997) and worsen the clinical course of schizophrenia, e.g., exacerbating positive and negative symptoms, increasing the risk of relapse, or hospitalization (Green, 2005).

Previous *in vivo* imaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) reported no difference in DAT bindings between control subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004) except for one study reporting lower binding in patients with schizophrenia as compared with controls (Mateos et al., 2007). However, those studies evaluated DAT binding only in the striatum, as DAT density in extrastriatal regions is very low (in a postmortem human study, [^{125}I]PE2I binding in the thalamus was reported to be 15% of that in the striatum and negligible in the cortex) (Hall et al., 1999). The recent development of [^{11}C]PE2I, which has high affinity ($K_i = 17$ nM) and selectivity (more than 30-fold for other monoamine transporters) for DAT, allows the evaluation of extrastiatal DAT bindings (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, we evaluated DAT binding in the striatal and extrastriatal regions of patients with schizophrenia using [^{11}C]PE2I.

2. Materials and methods

2.1. Subjects

Eight patients (age range 25–52 yr, mean ± SD: 36.5 ± 9.5 yr) diagnosed with schizophrenia or schizophreniform disorder according to DSM-IV criteria participated in this study. Four patients with schizophreniform disorder met the criteria for schizophrenia at six month follow-up. Exclusion criteria were current

* Corresponding author. Tel.: +81 43 206 3251; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

0022-3956/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2009.04.009

Table 1
Demographic and clinical characteristics.

	Controls	Patients
N	12	8
Age (years)	33.2 ± 12.0	36.5 ± 9.5
Gender (M/F)	10/2	6/2
Naïve/free		6/2
Duration of illness (months)		32.1 ± 42.8
PANSS (total)		77.8 ± 18.8
Positive		17.8 ± 4.8
Negative		18.9 ± 6.5
General		41.1 ± 10.8

Values are mean ± SD.

or past substance abuse, organic brain disease, or epilepsy. Demographic and clinical data are shown in Table 1. Six of the patients were antipsychotic naïve and two had been antipsychotic-free for at least six months before the PET scan. Three patients had taken benzodiazepines the night before the PET scan.

Psychopathological symptoms were assessed by three experienced psychiatrists on the same day as the PET scans using the Positive and Negative Syndrome Scale (PANSS), and consensus ratings were used. PANSS scores used were total score and subscores for positive symptom, negative symptom and general symptom.

Twelve normal control subjects (age range 23–56 yr, mean ± SD: 33.2 ± 12.0 yr) also participated. None of them had a history of psychiatric or neurological disorders, brain injury, chronic somatic illness, or substance abuse. None had taken any drugs within two weeks before the PET scan.

After complete description of this study, written informed consent was obtained from all subjects. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Data were collected from 4/2003 to 8/2006.

2.2. PET procedure

A PET scanner system, ECAT EXACT HR+(CTI-Siemens, Knoxville, TN, USA), was used for all measurements. A head fixation device was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source before each scan. A dynamic PET scan was performed for 90 min (20 s × 9, 1 min × 5, 2 min × 4, 4 min × 11, 5 min × 6) after intravenous bolus injection of 214.7 ± 13.7 MBq (mean ± SD) of [^{11}C]PE2I. The specific radioactivity of [^{11}C]PE2I was 344.5 ± 355.3 MBq/nmol. Injected dose and specific radioactivity between the control and patient groups were not significantly different (two-tailed *t*-test; $P = 0.15$ and $P = 0.16$, respectively). Since two previous quantitative studies of [^{11}C]PE2I had reported good reliability with scan times of 63 and 69 min, the scan time of 90 min was considered sufficient for estimation of DAT bindings especially in extrastriatal regions (Hirvonen et al., 2008; Jucaite et al., 2006). Magnetic resonance (MR) images of the brain were acquired with a 1.5 Tesla MR imaging system, Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images were obtained at 1 mm slices. All subjects were free of organic brain lesions.

2.3. Data analysis

All MR images were coregistered to the PET images using the statistical parametric mapping (SPM2) system. MR images were transformed into the standard brain size and shape by SPM2 (anatomic standardization). All PET images were also transformed into the standard brain size and shape using the same parameters as the MR image standardization. Thus, brain images of all subjects had the same anatomic format (Ito et al., 2008). Motion corrections were not made.

Regions of interest (ROIs) were drawn on all anatomically standardized PET images with reference to the T1-weighted MR images. ROIs were defined for the cerebellar cortex, caudate head, putamen, substantia nigra and thalamus (Fig. 1).

Binding potential (BP_{ND}) was calculated by the simplified reference tissue model (SRTM) method. The cerebellum was used as reference region because of its negligible density of DAT (Hall et al., 1999). In this study, the software package PMOD (PMOD Technologies, Zurich, Switzerland) was used to calculate BP_{ND}.

2.4. Statistics

Statistical analysis concerning the difference of BP_{ND} for each ROI between patients and controls was performed by two-tailed *t*-test. Correlations between BP_{ND} of patients with schizophrenia and age, duration of illness, and PANSS scores were evaluated using Pearson's correlation coefficient. In all analyses, $P < 0.05$ was considered significant.

3. Results

The BP_{ND} values of control subjects and patients with schizophrenia are shown in Table 2. The BP_{ND} value in the thalamus was significant higher in patients with schizophrenia than in con-

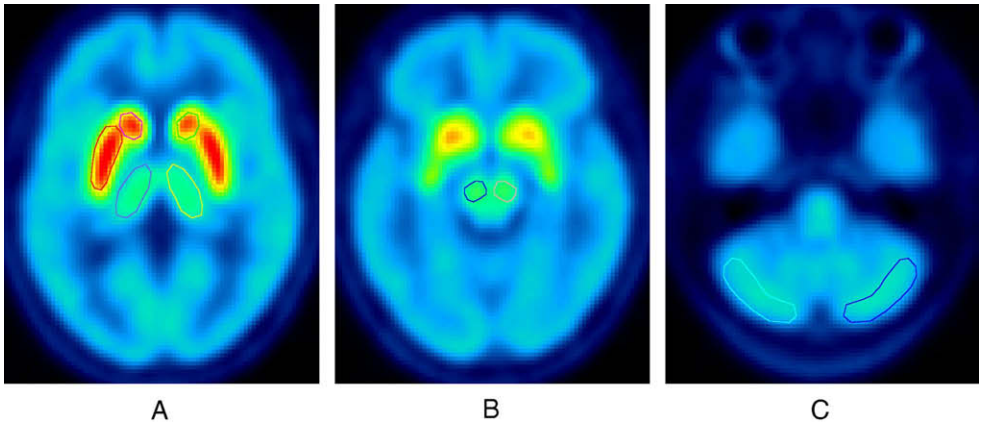

Fig. 1. Summated images of [^{11}C]PE2I with regions of interest. Average normalized images of twelve control subjects are shown at the level of caudate, putamen and thalamus (A), substantia nigra (B) and cerebellum (C).